**Supplementary Table One** Local guidelines for investigations in children with early developmental impairment and costs over time frame of study

|  |
| --- |
| **Blood samples**Full blood count £3.75 Zinc protoporphyrin / haematimics £13.79Renal function £3.47Liver function £3.47Thyroid function £5.94Bone profile (calcium and phosphate) £3.45Plasma amino acids £82.00\*Biotinidase £53.00\*Creatine kinase (boys only) £3.41Lead level £15\*Chromosome (pre 2012 - £120) or microarray (post 2012) £300.00\*Fragile X if suspected by family history £80.00\***Urine samples**Organic acids £82.00\*Glycosaminoglycans (if older than three months) £20.00\***Total cost of all tests on our guideline:** £669.28**Other recommendations (not studied in this article)**Audiology referralOphthalmology referral – not mandatory, to consider if concerns**Magentic resonance imaging under general anaesthetic** (not part of guideline but performed in 55% of cases and found to have high yield) £932.00\* |

\*Costs incurred to a district general hospital for test (as few hospitals seeing children with EDI have metabolic laboratories. All other, unasterisked, costs are local prices)

**Supplementary table 2:** Summary of genetic diagnoses made

|  |
| --- |
| **Diagnostic microarray results** |
| * Chromosome 1p36,13 deletion (3 cases)
* Chromosome 1q21 deletion
* Chromosome 1q21 duplication
* Chromosome 2p25 deletion
* Chromosome 2p16 deletion
* Chromosome 2q deletion
* Chromosome 4q33 deletion
* Chromosome 5q23 deletion (two cases)
* Chromosome 5q from q34 to q35
* Chromosome 5 microdeletion
* Chromosome 7q11 deletion
* Chromosome 7q35 deletion
* Chromosome 7p22 duplication
* Chromosome 10 duplication with breakpoints within q22.3 and q23.31
* Chromosome 11 deletion with breakpoints q14.1 and q22.1
* Chromosome 11p15 duplication
* Chromosome 12 duplication with breakpoints q14.1 and q15
* Chromosome 13q12 deletion
* Chromosome 15q11 deletion (four cases)
* Chromosome 15q13 deletion (four cases)
* Chromosome 15q11 deletion
* Chromosome 15 microduplication (three cases)
* Chromosome 16p11 duplication (three cases)
* Chromosome 16p13 duplication
* Chromosome 17q21 deletion
* Chromosome 17 duplication with breakpoints q11.1 and q12
* Chromosome 17q12 duplication
* Deletion of short arm of chromosome 18
* Chromosome 18q22 deletion
* Chromosome 22q11 duplication
* Chromosome 22q13 deletion
* Chromosome 22q13 deletion
* Chromosome Xq26 deletion
* Chromosome Xq24 deletion including UBE2a gene
* Chromosome 22q11 duplication
* Duplication long arm X chromosome including PLP1 gene
* Duplication of X chromosome Xq28 (2 cases)
 |
| **Single gene or clinical diagnoses**  |
| Bardet Biedl Syndrome - 5 cases Neurofibromatosis type 1 - 3 casesSLC2A1 (GLUT1) mutation - 2 casesRett Syndrome - 1 caseAngelman syndrome - 1 caseKabuki syndrome - 2 cases (1 genetic, 1 clinical)Cornelia de Lange syndrome - 1 caseKleefstra syndrome - 1 caseCreatine transport deficiency - 1 caseRYR1 mutation – 1 caseASPM microcephaly mutation - 1 caseUBE2A mutation - 1 casePHGDH mutation - 1 caseCASK1 mutation - 1 caseCOL4A1 mutation - 1 caseSLC9A6 mutation - 1 caseNRXN1 mutation - 1 casePLP1 (Pelizaeus-Merzbacher disease) - 1 caseDGUOK (mitochondrial depletion) mutation - 1 caseSLC7A7 mutation (lysinuric protein intolerance) - 1 casePDHA1 mutation (pyruvate dehydrogenase deficiency) - 1 caseSLC6A8 mutation (creatine transport deficiency) - 1 caseETHE1 mutation (ethylmalonic aciduria) - 1 caseTetrasomy 18p - 1 caseSotos syndrome (clinical diagnosis) - 1 caseOdho symdrome (clinical diagnosis) - 1 caseAtypical ataxia telangiectasia (clinical diagnosis, gene negative) - 1 caseFetal alcohol syndrome - 1 case |

**Supplementary figure one:** a) The frequency with which additional features were seen in participants; b) the proportion of children with a diagnosis according to additional features; c) the proportion of children with a diagnostic microarray according to additional features; d) the proportion of children with a diagnostic MRI according to additional features